CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DIMETHOXANE

Chemical Code # 1359, Tolerance # 50841
SB 950 # 212

11/10/99

I. DATA GAP STATUS

Chronic toxicity, rat:	Inadequate study; no adverse effect indicated[1]
Chronic toxicity, dog:	No study on file[1]
Oncogenicity, rat:	Inadequate study; no adverse effect indicated[1]
Oncogenicity, mouse:	Inadequate study; possible adverse effect indicated[1]
Reproduction, rat:	No study on file[1]
Teratology, rat:	No data gap; no adverse effect
Teratology, rabbit:	No study on file[1]
Gene mutation:	No data gap; no adverse effect
Chromosome effects:	No data gap; potential adverse effect
DNA damage:	No data gap; no adverse effect
Neurotoxicity:	No study on file[1]

Toxicology one-liners are attached.

All record numbers through 164566 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: t175425n
Eya, 11/10/99

[1] New active ingredient, Dimethoxane, submitted as an antimicrobial for terrestrial non-food use. These studies are not required at this time.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

001; 75642; "Toxicology and Carcinogenesis Studies of Dimethoxane (CAS No. 828-00-2) (Commercial Grade) In F344/N Rats and B6C3F_1 Mice (Gavage Studies)" (K. Abdo, Battelle Columbus Lab., Columbus, OH., and National Toxicology Program, Research Triangle Park, NC.,NIH Publication No.:89-2809, 09/89). Sixty rats/sex/group were treated with Dimethoxane (Lot # 6270-79; >80% purity) by oral gavage at concentrations of 0, 62, 125 or 250 mg/kg ((M): 0, 62, 125 mg/kg/day; (F): 0, 125, 250 mg/kg/day, respectively, 5-day/week) for 103 weeks. Ten animals/sex/group were sacrificed for hematology, necropsy, and histopathological examination after 15-months of treatment. No compound related clinical signs were observed throughout the study. Body weight and survival of dosed male and female rats were similar to those of vehicle controls. Acanthosis and hyperkeratosis were increased in high dose rats. Acanthosis and hyperkeratosis often occurred together and consisted of focal thickening of the stratified squamous epithelium with the accumulation of keratin on the surface, often near the junction of the forestomach and the glandular stomach. Squamous cell papillomas were seen in one high dose male and female. Under the conditions of this 2-year corn oil gavage study, there was no evidence of carcinogenic activity in F344/N rats at the dosage of dimethoxane used for treatment. **No adverse effect. Chronic NOEL**: M: 62.5 mg/kg/day and F: 125 mg/kg/day (based on the incidence of abnormal histological findings in the forestomach/stomach in the high dose male (125 mg/kg/day) and high dose females (250 mg/kg/day)), 5-days/week for 103 weeks; **Study uncceptable** and not upgradeable due to missing parameters required for a combined chronic toxicity/oncogenicity study. (Eya, 09/08/99)

CHRONIC TOXICITY, RAT

See Combined, Rat

CHRONIC TOXICITY, DOG

No study submitted

ONCOGENICITY, RAT

See Combined, Rat

ONCOGENICITY, MOUSE

001; 75642; "Toxicology and Carcinogenesis Studies of Dimethoxane (CAS No. 828-00-2) (Commercial Grade) In F344/N Rats and B6C3F_1 Mice (Gavage Studies)" (K. Abdo, Battelle Columbus Lab., Columbus, OH., and National Toxicology Program, Research Triangle Park, NC.,NIH Publication No.:89-2809, 09/89). Sixty mice/sex/group were treated with Dimethoxane (Lot # 6270-79; >80% purity) by oral gavage at concentrations of 0, 250, or 500 mg/kg, 5-day/week for 103 weeks. Ten animals/sex/group were sacrificed for hematology, necropsy, and histopathological examination after 15-months of treatment. No compound related clinical signs were observed throughout the study. Body weight and survival of dosed mice were similar to those of vehicle controls. After 15 months, harderian gland neoplasm were seen in one high dose male and 2 high dose female mice. However, no increase in the incidence of harderian gland neoplasm was seen at 2 years. Acanthosis of forestomach was seen in almost half of the mice in the high dose groups. Inflammation, acanthosis with hyperkeratosis, and focal hyperplasia occurred at increased incidences in the forestomach of dosed mice. In male mice, there was a slight dose-related increase in squamous cell papillomas, and squamous cell carcinomas,

however, pair-wise comparison between vehicle control and low or high dose male mice were not statistically significant. No increased incidences of forestomach neoplasms were seen in female mice. The carcinogenic activity of Dimethoxane was either equivocal (in male) or not evident (in female) in $B6C3F_1$ mice receiving doses of 250 or 500 mg/kg/day. **Possible adverse effect:** equivocal evidence of squamous cell papillomas in male mice. **Chronic NOEL**: M/F: < 250 mg/kg (based on increased incidence of acanthosis, hyperkeratosis, chronic active inflammation, and focal hyperplasia in dosed mice, and squamous papillomas in male mice.) treated for 5-days/week and 103 weeks; **Study unacceptable** and not upgradeable due to missing parameters required for an oncogenicity study. (Eya, 09/08/99)

REPRODUCTION, RAT

No study submitted

TERATOLOGY, RAT

006; 164566; "A Teratogenicity Study in Rats With Giv 2-0494" (R. E. Schroeder, Bio/dynamics, Inc. East Millstone, NJ., Project No.: 88-3322, 06/02/89). Twenty four mated females/group were treated by oral gavage with 0, 60, 300, and 900 mg/kg/day of Giv 2-0494 (Lot # 5935-88; purity: 84.2%) during 6-15 gestation days. No mortality resulted from the treatment, however, 2 deaths due to dosing injury occurred at 900 mg/kg/day (1 female found dead on day 10 of gestation and another female sacrificed moribund on day 13 of gestation). The 60 and 300 mg/kg/day dose levels were not maternally toxic, embryotoxic, fetotoxic or teratogenic. The only maternal effect seen at these dose levels was an increased incidence of females with excessive salivation during the treatment period (i.e., 0/25 (control) vs. 15/24 (300 mg/kg/day) and 26/26 (900 mg/kg/day), $p < 0.05$). At the 900 mg/kg/day dose level, maternal toxicity was evident from the statistically significant reduction in weight gain and food consumption. No other maternal effects were seen at the 900 mg/kg/day dose level, and this dose level was not considered to be embryotoxic, fetotoxic or teratogenic. **No adverse effects. Maternal NOEL: 60 mg/kg/day (based on increased salivation compared to the control group); **Developmental NOEL:** 900 mg/kg/day; **Study acceptable.** (Eya, 08/24/99).

TERATOLOGY, RABBIT

No study submitted

GENE MUTATION

004; 164561; "Mutagenicity Test on GIV 2-0494 in the Ames Salmonella/Microsome Reverse Mutation Assay" (D. C. Valentine; T. E. Lawlor, Hazleton Laboratories America, Inc. Kensington, MD., HLA Study No.: 10696-0-401, 05/05/89). *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 were treated for 48-72 hours at 37 $\pm$ 2 ^{o}C with GIV 2-0494 (Lot # 5935-88; 93% purity) at concentrations ranging from 0.01 to 10 uL/plate test article with and w/o activation in 2 trials (4 trials for TA 100). Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated. Study Acceptable. (Eya, 07/27/99)

001; 75642; "Toxicology and Carcinogenesis Studies of Dimethoxane (CAS NO. 828-00-2) (Commercial Grade) in F344/N Rats and $B6C3F_1$ Mice (Gavage Studies)" (K. Abdo, National Toxicology Program, Research Triangle Park, NC.,NIH Publication No.:89-2809, 09/89). *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated for 48 hours at 37 ^{o}C with Dimethoxane (Lot # 6270-79; >80% purity) at concentrations ranging from 33 to 6666 ug/plate test article with activation in 2 trials, and w/out activation 1 trial (3 trials for TA 100) with 20-minutes preincubation before plating. Each test consisted of triplicate plates of concurrent positive and negative controls and of at least 5 doses of the study chemical. An Aroclor 1254-induced male

Sprague Dawley rat or Syrian hamster liver S9 fraction was used to metabolize the test material. Dimethoxane was mutagenic when tested with a preincubation protocol in TA100 in the presence of S9, and it was not mutagenic in strains TA98, TA1535, or TA1537 w/ or w/out S9. Not acceptable but possibly upgradeable with submission of the full study report. (Eya, 08/31/99).

001; 75642; "Toxicology and Carcinogenesis Studies of Dimethoxane (CAS NO. 828-00-2) (Commercial Grade) in F344/N Rats and B6C3F_1 Mice (Gavage Studies)" (K. Abdo, National Toxicology Program, Research Triangle Park, NC.,NIH Publication No.:89-2809, 09/89). The assays for gene mutation and chromosomal translocation induction were performed using adult Canton-S wild-type males at Dimethoxane concentration of 6000-12,500 ppm. Initially, study chemicals were assayed in the sex-linked recessive lethal (SLRL) test by feeding for 3-days to the males that were not more than 24 hours old. If no response was obtained, the chemical was retested by injection into adult males. If either route of administration produced a positive result, the chemical was assayed for induction of reciprocal translocation (Rts) under the same method of exposure. Dimethoxane induced sex-linked recessive lethal mutations in Drosophila when administered by abdominal injection to the adult Canton-S males. No induction of reciprocal translocations was observed. Not acceptable but possibly upgradeable with submission of the full study report. (Eya, 09/01/99)

CHROMOSOME EFFECTS

****004; 164562;** "Mutagenicity Test on GIV 2-0494 in an *In Vitro* Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells" (H. Murli, Hazleton Laboratories America, Inc. Kensington, MD., HLA Study No.: 10696-0-437, 04/24/89). Chinese hamster ovary (CHO-WBL) cells were exposed to GIV 2-0494 (Lot # 5935-88; purity: 93.0%) at concentrations ranging from 0.166 to 4990 ug/mL tested with and w/out metabolic activation (range-finding assay). The chromosome aberration assay w/out activation was performed at concentrations of 2.27-50.4 ug/mL, with exposure time of 7.25 hours to the test substance, and harvest at 10 hours. The assay with activation was performed by incubating the cells with S9 and test substance for 2 hours at concentrations of 25.2-101 ug/mL (10 hour harvest) and 100-300 ug/mL (20 hour harvest), due to the cell cycle delay which was found in the range-finding study at 166 ug/mL. Incubations were performed at 37 ^{o}C with duplicate cultures/treatment level. An Aroclor 125-induced rat liver S9 fraction was used to activate the test material. An increase in the percentage of cells with chromosomal aberrations was noted in the assay with activation for the treatment levels of 100-225 ug/mL ($p < 0.01$). No treatment-related effects were evident in the non-activated samples. **Potential adverse effect:** increased percentage of cells with chromosomal aberrations under conditions of activation. **Study acceptable.** (Eya, 08/05/99).

001; 75642; "Toxicology and Carcinogenesis Studies of Dimethoxane (CAS NO. 828-00-2) (Commercial Grade) in F344/N Rats and B6C3F_1 Mice (Gavage Studies)" (K. Abdo, National Toxicology Program, Research Triangle Park, NC.,NIH Publication No.:89-2809, 09/89). Chinese hamster ovary (CHO) cells were exposed to Dimethoxane (Lot # 6270-79; >80% purity) at concentrations ranging from 0.36 to 198 ug/mL, tested with and w/out metabolic activation (S9). The test for induction of sister chromatid exchanges (SCEs) was performed at concentrations of 0.36-12.6 ug/mL (w/out S9) and 11-110 ug/mL (w/ S9). The test for induction of chromosomal aberrations in CHO cells was performed at concentrations of 12.6-22.7 ug/mL (w/out S9) and 126-198 ug/mL (with S9). The S9-fraction from an Arochlor 1254-induced male Sprague Dawley rat liver was used to activate the study compound. Dimethoxane induced a significant increase in SCEs within a dose range of 1.1-12.6 ug/mL (w/out S9) and 11-110 ug/mL (w/ S9). Dimethoxane also induced chromosomal aberrations and cell cycle delay in CHO cells w/ and w/out S9. Doses of 20.2-22.7 ug/mL w/out S9 produced abnormal metaphases in 100% of cells scored, and chromosomal aberration in 75% of cells exposed to $\geq$ 176 ug/mL Dimethoxane w/S9. Not acceptable but possibly upgradeable with submission of the full study report. (Eya, 09/01/99).

DNA DAMAGE

004; 164564; "Mutagenicity Test on GIV 2-0494 in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay" (M. A. Cifone, Hazleton Laboratories America, Inc. Kensington, MD., HLA Study No.: 10696-0-447, 04/11/89). Primary rat hepatocyte cultures were exposed to GIV 2-0494 (Lot # 5935-88; purity: 93.0%) at concentrations ranging from 0.506 to 5060 ug/mL for 20.7 hours at 37 ^{o}C. Vehicle control (Acetone 0.05%) and positive control (2-Acetylaminofluorene, 2-AAF: 4.48 x 10^{-7} M; 0.10 ug/mL) cultures were included in the assay. There were 3 cultures per treatment level. There was no treatment-related increase in unscheduled DNA synthesis. **No adverse effect indicated. Study acceptable. (Eya, 08/10/99)

NEUROTOXICITY

No study submitted

SUBCHRONIC STUDY

50841-005; 164565; "A Subchronic (3-Month) Dermal Toxicity Study of DXN in the Rat" (D. L. Blaszcak, Pharmaco LSR, Inc., East Millstone, NJ., Study No.: 92-2203, 09/07/93). GIV-Gard DXN^{R} (Lot # 5314-92; purity: 87.7%) was administered dermally to 60 Sprague-Dawley CD^{R} rats (10/sex/ group) for 6 hours per day, 5 days per week, at dose levels of 100, 300, and 1000 mg/kg/day for a period of 90 days. Control animals (10/sex) were sham-treated. Except for 1 control male found dead, and 1 mid-dose male sacrificed for humane reasons, all animals survived the study and were free of signs of systemic toxicity. Little or no test material-related irritation was seen in any animals up to low- and mid-dose in females and males, respectively. The dermal responses, possibly related to test material application observed at 1000 mg/kg/day (M:1/10, F:2/10), were limited to eschar (scabbing) and superficial necrosis with exfoliation. All animals were free of ocular abnormalities. Mean body weight of mid- and high-dose males were slightly lower than the control animals, and were 5 to 8% lower than mean control weight values by study termination. Mean body weights of the low-dose males and all females were comparable to the controls. No significant changes in hematology, clinical chemistry values, mean organ weight, organ/body ratio, organ/brain ratio, or macroscopic findings were observed, which were related to the dermal application of test material. Microscopic observation revealed scattered foci of hepatocellular necrosis accompanied by acute/ subacute inflammation and hemorrhages of liver were found at 300 mg/kg/day (F: 3/10) and at 1000 mg/kg/day (F:5/10). **No adverse effects**. Systemic NOEL (M): 300 mg/kg/day and (F): 100 mg/kg/day, based on significant decrement in body weight gain in males at 1000 mg/kg/day and microscopic liver changes in females at 300 and 1000 mg/kg/day from 5 days/week, 13 week dermal administration. Dermal NOEL (M/F) was not determined because the water used to clean the application sites reacted with the test material to produce dermal irritation during the first three weeks of the study. Therefore, the use of water to clean the application sites was discontinued after week 1. **Acceptable**. (Eya, 08/13/99)